UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/800,322	03/12/2004	Robert James	17530	2289

23389 7590 12/01/2010

SCULLY SCOTT MURPHY & PRESSER, PC
400 GARDEN CITY PLAZA
SUITE 300
GARDEN CITY, NY 11530

EXAMINER	
SWITZER, JULIET CAROLINE	

ART UNIT	PAPER NUMBER
1634	

MAIL DATE	DELIVERY MODE
12/01/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/800,322	JAMES ET AL.	
	Examiner	Art Unit	
	Juliet C. Switzer	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 October 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6-8,13 and 16-83* is/are pending in the application.

4a) Of the above claim(s) *2-4,6-8,16-31 and 34-82* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,13,32,33 and 83* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Examiner's exhibits 1, 2, and 3*.

DETAILED ACTION

1. Currently, claims 1-4, 6-8, 13, 16-83 are pending. Claims 1, 13, 32, 33, and 83 are under prosecution. All other claims are with drawn as being drawn to non-elected inventions.

2. Claim 16 was amended so that it no longer reads on the elected sequence combination, and now stands withdrawn. Rejoinder of the additional combinations which require SEQ ID NO: 7 will be considered only when there are allowable claims.

Claim Objections

3. Claims 32, 33, and 83 are objected to because they recited non-elected subject matter in the alternative. Applicant indicated that the non-elected subject matter is being maintained so that it can be considered upon a finding of allowable subject matter (paper filed 10/15/10, page 20). Rejoinder will be considered when appropriate.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1, 13, 32, 33 and 83 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims appear to be missing an essential step. For example, claim 1 recites in the preamble that it is "A method for determining the onset of colorectal adenoma" yet it includes only a single step of measuring the level of a expression of particular nucleic acid molecules. There is no step that actually results in the determination of the onset of colorectal adenoma.

The examiner has suggested an allowable claim at the end of this office action. That claim is free of this problem.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1, 13, 32, 33, and 83 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for

A method for determining an increased likelihood of the presence of colorectal adenoma in a human, said method comprising

measuring the level of an mRNA which comprises the RNA equivalent of SEQ ID NO: 7 in a gastrointestinal tract sample from said human and

determining an increased likelihood of the presence of colorectal adenoma when the level of said mRNA is increased in said human relative to the normal level of said mRNA in gastrointestinal tract samples from healthy individuals,

does not reasonably provide enablement for methods which detect any other transcription or translation products, methods which utilize other samples, or methods for the positive detection of colorectal adenoma. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

Claim 1 recites a method for determining the onset of colorectal adenoma. Thus, the nature of the invention requires that the recited method actually determine the onset of colorectal adenoma.

Further, the claim encompasses measuring the level of expression of (i) an mRNA which comprises the RNA equivalent of SEQ ID NO: 7 or (ii) the protein encoded by the mRNA that comprises the RNA equivalent of SEQ ID NO: 7. "Measuring the level of expression" is understood in light of the specification to be a measurement of transcription or translation of a nucleic acid molecule- that is measuring mRNA products or measuring expressed protein products (p. 23 of specification). For this portion of the claim, measuring the level of expression encompasses measuring expression of an mRNA or protein product of any mRNA that comprises the RNA equivalent of SEQ ID NO: 7.

Claim 1 requires that the sample is a blood, serum, stool or gastrointestinal tract sample.

The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The dependent claims recites a further limitation, for example, wherein the level of upregulation is 10-100 fold the normal level (claim 5), wherein the subject of detection is the expression product of said nucleic acid sequence (claim 13), wherein the method is directed to monitoring for the onset or progression of said adenoma in said human (claim 32), wherein the sample is of colorectal origin or a biopsy sample (claim 33), and wherein the adenoma is a tubular adenoma, tubulovillous adenoma, or a villous adenoma (claim 83), but all of these claims still encompass breadth and subject matter which is problematic and discussed in this office action.

The examples in the specification teach differential display analysis of samples of adenoma and normal tissue obtained from patients undergoing colonoscopy, comparison of the isolated sequences to nucleic acid databases housed by NCBI using BLAST, and RT-PCR confirmation of the differential expression of the isolated molecules (examples 1-3). Example 4 describes the testing of 71 colon adenoma tissue samples by quantitative RT-PCR and comparison of the expression levels to the mean expression levels of normal tissues. From these results a "fold increase" was tabulated for each isolated nucleic acid. The specification teaches on page 79, Table 2 that SEQ ID NO: 7 corresponds to Adenoma Marker clones named 12-2f and 8-2d.

Table 3 from the specification teaches that clone 8-2d was, on average, upregulated 50 fold relative to the mean expression levels of normal tissues, and that clone 12-2f was on average, upregulated 45 fold relative to the mean expression levels of normal tissues (table 3), and that both clones were upregulated greater than 5-fold in 100% of the adenoma tissues (table

5). The specification also teaches, however, that 19% of the normal tissue samples showed upregulation of both of these clones (table 6 and table 7).

There is no external working example which validates the use of SEQ ID NO: 7 as a marker for colorectal adenoma, but the declaration filed 3/26/10 provide data which validate the finding that SEQ ID NO: 7 has increased expression in colorectal adenoma colorectal samples versus healthy control tissue (see Exhibit 5, figure 5).

The data given in the tables is given as averages- the mean fold increase in adenoma samples versus the mean expression level of normal tissues. For both normal and adenoma means, no mention is given in the specification as to the ranges of observed values, the variation among samples or any formal statistical analysis to determine if the differences observed between types can be attributed to sample effects of to the chance of error. This is a significant absence given that the specification teaches that 19% of normal tissues also over expresses both clones, and because the claims positively state that they are methods for detecting the presence of onset of colorectal adenoma.

Since the breadth of the claims encompasses the detection of any mRNA transcript or encoded protein that is expressed from an mRNA comprising the RNA equilavent SEQ ID NO: 7, it is significant to note that the specification does not provide any evidence or guidance as to molecules that can be detected as differentially expressed other than the mRNA equivalent of SEQ ID NO: 7. There is no guidance as to what protein, if any is encoded by the mRNA equivalent of SEQ ID NO: 7 or by an nucleic acid which comprises SEQ ID NO: 7. In the declaration filed 3/26/10, applicant demonstrates in Figure 1, Exhibit 3, that instant SEQ ID NO: 7 occurs in an intron of gene KIAA1199. It appears, therefore, that the mRNA represented by

the cDNA of SEQ ID NO: 7 does not encode any protein product that has been disclosed. The recitation of measuring the expression level of an mRNA or the protein encoded by said mRNA, wherein the mRNA comprises the RNA equivalent of SEQ ID NO: 7 appears to exclude the detection of a primary mRNA that encodes the KIAA1199 protein and also the detection of the KIAA1199 protein itself as indicators of the presence of colorectal adenoma since the mRNA commonly referred to as KIAA1199 and the encoded protein have no significant identity with SEQ ID NO: 7 or any protein encoded by SEQ ID NO: 7. The declaration also teaches that there are multiple transcripts produced from the genomic region of human chromosome 15 that encodes KIAA1199 (see Exhibit 2 of the declaration), and that SEQ ID NO: 7 is but one of these expression products (see paragraph 7), but the specification provides no guidance as to the identity of these transcripts, what proteins or protein fragments they encode, and which are differentially expressed relative to normal tissue in colorectal adenoma tissue.

The specification exemplifies that clones 8-2d and 12-2f have levels of expression higher than five fold versus average expression in normal control tissue in 100% of adenoma tissues, but the specification does not demonstrate that high levels of expression could be observed in other types of tissues- blood or serum or stool- or even that if it were that it would indicate colorectal adenoma.

The specification does not demonstrate the detection of SEQ ID NO: 7 translation products, nor does it demonstrate that these putative translation products are detectable at different levels that could be used as set forth in the claimed methods. In fact, it appears from the declaration, that the mRNA detected whose cDNA is disclosed as SEQ ID NO: 7 might not

have an expression product, per se, since it is an mRNA that would have been transcribed entirely from an intron.

The guidance provided by the specification amounts to an invitation for the skilled artisan to try and follow the disclosed instructions to make and use the claimed invention commensurate in scope with the claims.

Because the claims encompass the analysis of translation products of mRNA molecules that comprise the RNA equivalent SEQ ID NO: 7, while the specification provides only an example of the analysis of mRNA levels by differential display and quantitative RT-PCR of an mRNA, presumably the RNA equivalent of SEQ ID NO: 7, it is relevant to point out the unpredictability as to whether or not a measure of any nucleic acid expression is indicative of the level of protein in a sample. First, it is noted that based on applicant's declaration, it appears that the transcript that applicant disclosed as detecting (i.e. consisting of the RNA equivalent of SEQ ID NO: 7) may or may not in fact get translated into a protein. Further, though, it is noteworthy that the post-filing art of Chan teaches that cells have elaborate regulatory mechanisms at the level of transcription, post-transcription, and post-translation (p.1, last paragraph), and that transcript and protein abundance measurements may not be concordant (p.3, sixth full paragraph). Thus it is unpredictable as to whether or not the results pertaining to nucleic acid expression, as presented in the instant specification, would be applicable to methods requiring or encompassing the analysis of a protein samples.

The claims also encompass making a positive detection that adenoma is present. There no guidance or showing that demonstrates the range of values observed in the adenoma versus normal samples, and the specification teaches that at least 20% of the normal samples

overexpressed the subject clones. It is highly unpredictable, therefore, what level of expression of SEQ ID NO: 7 must be observed in order for one to successfully conclude that adenoma is present, as recited in the preamble of the claims. In order to use the claimed invention commensurate in scope with the claims one would have to undertake an extensive amount of unpredictable experimentation.

In order to practice the invention commensurate in scope with the claims, one would have had to determine whether or not the mRNA comprising the RNA equivalent of SEQ ID NO: 7 encoded a protein product. Further, one would have had to determine which tissues the transcript comprising SEQ ID NO: 7 and any other transcripts or proteins expressed from a nucleic acid comprising SEQ ID NO: 7 or the complement thereof are expressed in tissues other than tissue obtained from colonoscopy, and when expressed in these tissues, which expression levels remain indicative of colorectal adenoma. Further, since the claims state that they are directed towards actually detecting the onset of colorectal adenoma, and since the specification teach that at least 19% of healthy individuals overexpressed the transcript comprising the mRNA equivalent of SEQ ID NO: 7, extensive experimentation would be required to determine which levels of SEQ ID NO: 7 expression actually positively identify the presence of disease. The quantity of experimentation in this area is extremely large since there are significant number of parameters which would have to be studied. Furthermore, one would have to discover the expression product or products of SEQ ID NO: 7 and establish reliable methods of detection and that this product is in fact translated in patterns similar to the transcription patterns of the observed mRNA. This would require extensive experimentation and specific guidance, with many intervening steps, upon effective reduction to practice, not providing any guarantee of

success in the succeeding steps, which are not routine, and an artisan of skill would not have known at the time of invention.

In the instant case, as discussed above, in a highly unpredictable art where an increased expression of a DNA marker is asserted to be associated with colorectal adenoma, the specification provides minimal guidance for a specific example (the expression levels of two clones in colorectal adenoma tissue) and insufficient guidance to support the full scope of the claims which includes detection of a variety of possible transcripts and protein products, in a variety of possible tissue types.

Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of a working example and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Response to Remarks

The rejection has been modified to address the amended claims.

Applicant traverses the rejection insofar as it applies to the amended claims.

The traversal has been carefully considered but is not persuasive.

Applicant states that the examiner concludes that the mRNA detected (i.e. SEQ ID NO: 7) "does not code for an actual protein product." To the contrary, the examiner's position is that it is unknown based on the specification (1) if the "intronic mRNA" is actually translated and (2) if that translation product is also present at differential levels that might be diagnostic of the

onset of colorectal adenoma. Further, it is the examiner's position that the data in the specification and art do not support an assertion that an mRNA comprising the RNA equivalent of SEQ ID NO: 7 encodes the protein known in the art as KIAA1199.

There has been considerable discussion on this record as to the relationship between instant SEQ ID NO: 7 and a molecule referred to in prior and post-filing date literature as KIAA1199. Applicant has provided evidence to show that instant SEQ ID NO: 7 matches a portion of human genomic sequence that occurs between exons 1 and 2 of the genomic KIAA1199 sequence based on the exon/intron designations defined by the NCBI database (see declaration filed 3/26/10, at paragraph 6). However, neither the declaration nor applicant's arguments address whether or not the database information used to make this determination was available before the filing of the instant application. Either way, this information is not disclosed in the specification, and is in fact supplementary to the specification. It does not flow from the teachings of the specification. Regarding MPEP 2164.05, it is noted that the guidance sets forth:

> "To overcome a prima facie case of lack of enablement, applicant must demonstrate by argument and/or evidence that the disclosure, as filed, would have enabled the claimed invention for one skilled in the art at the time of filing. This does not preclude applicant from providing a declaration after the filing date which demonstrates that the claimed invention works. However, the examiner should carefully compare the steps, materials, and conditions used in the experiments of the declaration with those disclosed in the application to make sure that they are commensurate in scope; i.e., that the experiments used the guidance in the specification as filed and what was well known to one of skill in the art. Such a showing also must be commensurate with the scope of the claimed invention, i.e., must bear a reasonable correlation to the scope of the claimed invention"

Applicants and the Pedersen declaration state that NCBI's "AceView database" discloses experimentally identified cDNA clones transcribed from intronic sequences, and that SEQ ID NO: 7 is simply another of such transcripts (declaration filed 3/26/10, at paragraph 7). However,

it is noted that SEQ ID NO: 7 is a DNA sequence, so presumably it is a cDNA of such a transcript (which would be an mRNA).

The declaration states that the experimental data in Exhibit 3 are provided to show that SEQ ID NO: 7 is in fact a transcript of the KIAA1199 gene (paragraph 9). The declaration states that Figure 1 in Exhibit 3 shows that RNA samples derived from exons 1 and 2 of the KIAA1199 gene, which flank SEQ ID NO: 7, show upregulation in colorectal neoplasia; this finding is not relevant to the instant claims which are directed towards onset of colorectal adenoma. This figure does not provide any actual data regarding expression of an mRNA which comprises the mRNA equivalent of SEQ ID NO: 7, since none of the exons tested is within the mRNA equivalent of SEQ ID NO: 7. Figure 3 shows the results from a PCR experiment with RNA extracted from colon tissue specimens using one primer from within SEQ ID NO: 7 and one primer from within KIAA1199 exon 2, and PCR products were observed. The declarant concludes, based on this result that "Clearly, SEQ ID NO: 7 is an integral part of the genomic sequence of KIAA1199, and KIAA1199 is transcribed with the SEQ ID NO: 7 sequence forming part of the mRNA (declaration, paragraph 10)." However, there is not evidence to suggest that an mRNA that comprises the mRNA equivalent of SEQ ID NO: 7 actually encodes the protein which is referred to in the prior art and declaration as KIAA1199.

None of these experiments use guidance provided in the specification to make their points about the function of any molecule which is the RNA equivalent of SEQ ID NO: 7.

The data presented in the declaration is all entirely supplementary to the instant specification. Second, as previously noted, it is not clear on this record how much of the data relied upon from the NCBI databases would have been available to one having ordinary skill in

the art. Third, there is no discussion in the instant specification to suggest that instant SEQ ID NO: 7 is an intronic transcript of KIAA1199.

The instant claims encompass measuring the level of expression of a an mRNA or the protein encoded by said mRNA wherein said mRNA comprises the RNA equivalent of SEQ ID NO: 7. The specification teaches that measuring the level of expression can include measuring transcribed sequences (i.e. mRNA) or measuring translation products. It is clear from the specification, and supported by examples in the declaration that mRNA comprising the RNA equivalent of SEQ ID NO: 7 or its complement was detected as being more highly expressed in colorectal adenoma tissues relative to healthy control tissue. There is no guidance in the specification to suggest that the mRNA detected was longer than that given in SEQ ID NO: 7, and in particular, no exon sequence from KIAA1199 is given in the specification.

The evidence on the record does not support an assertion that the mRNA comprising the RNA equivalent of SEQ ID NO: 7 encodes the protein which is referred to in the specification, declaration and prior art as KIAA1199.

(1) The examiner provides with this office action a copy of GenBank EAW99111 which provides the amino acid sequence of the protein referred to in the art as KIAA1199. (see Examiner's exhibit 1).

(2) The examiner attempted to align this protein with proteins that would be encoded by the mRNA equivalent of SEQ ID NO: 7. There were no significant matches. (See Examiner's exhibit 2).

(3) The examiner subjected instant SEQ ID NO: 7 to a six frame translation tool. In every possible frame SEQ ID NO: 7 and its complement encode for sequences that have many

possible stop codons. None of the suggested protein translations results in the protein identified as KIAA1199 in the prior or post-filing date art. (See Examiner's exhibit 3).

Applicant has indeed established that instant SEQ ID NO: 7 is transcribed from a portion of the "KIAA1199 gene" that has been considered an intron. Applicant has not established that any transcript which comprises the RNA equivalent of SEQ ID NO: 7 encodes a protein referred to in the prior or post-filing art as KIAA1199 protein, nor have they established that any protein translated from an mRNA that comprises the mRNA equivalent of SEQ ID NO: 7 is differentially expressed in the same way that SEQ ID NO: 7 itself is differentially expressed.

Applicant's particular remarks are addressed as follows:

On page 22, Applicant points out that SEQ ID NO: 7 was identified based on differential expression, and must appear in the mRNA transcript. It is not disputed that the mRNA equivalent of SEQ ID NO: 7 was detected as a differentially expressed mRNA. The examiner has suggested an allowable claim based on the observation disclosed in the specification and supported by the declaration.

Applicant further states on page 22 that "mRNA is generally synthesized for the purpose of subsequent translation to a protein." Generally, this is true. However, the level of translation is not always concordant with the mRNA expression level, and so it remains unpredictable if the protein encoded by the mRNA equivalent of SEQ ID NO: 7 would be indicative of the onset of colorectal adenoma, as discussed in the rejection. Further, there is no evidence as to what protein is actually translated from the mRNA equivalent of SEQ ID NO: 7. A six frame translation of SEQ ID NO: 7 reveals a variety of possible proteins, with each frame translation

including multiple stop codons throughout the potential mRNA (see attached six frame translation of SEQ ID NO: 7).

Applicant further directed the examiner to the data provided in Exhibit 4 of the Pedersen Declaration which applicant states demonstrate that increased levels of the translation product of a SEQ ID NO: 7 containing gene was detectable in stool samples of patients with colorectal adenoma. The instant claims require measuring the level of the protein encoded by an mRNA wherein said mRNA comprises the RNA equivalent of SEQ ID NO: 7. The only mRNA disclosed in the specification that comprises the RNA equivalent of SEQ ID NO: 7 is a molecule consisting of the RNA equivalent of SEQ ID NO: 7. The possible proteins encoded by this molecule have very little identity to the protein referred to in the prior art as KIAA1199 (see BLAST alignment included with this office action). Exhibit 4 in the declaration refers to an indirect ELISA using a monoclonal anti-KIAA1199. First, there is no evidence that the antibody used in the experiments were available in the prior art at the time of filing and there is no guidance in the specification directing one having ordinary skill in the art that the anti-KIAA1199 antibody might detect a protein encoded by the mRNA equivalent of SEQ ID NO: 7. Second, it appears that the declaration is using KIAA1199 to refer to the protein named with this name in the post-filing date art, see for example GenBank EAW9911.1 whose earliest date of availability was 12/18/06. This molecule is not encoded by the mRNA equivalent of SEQ ID NO: 7, and so the data given in Exhibit 4 of the declaration are not commensurate in scope with the instant claims.

In the section bridging pages 22-23 Applicant states that the notion that detection of a biomarker in tissue samples translates to detectable changes in blood or serum levels is well

documented and amply supported by the art, and confirmation thereof would not require undue experimentation. To support their position, applicant again refers to detection of the expression of the KIAA1199 protein in stool and plasma samples. First, there is no evidence that the antibody used in the experiments were available in the prior art at the time of filing, and there is no guidance in the specification directing one having ordinary skill in the art that the anti-KIAA1199 antibody might detect a protein encoded by the mRNA equivalent of SEQ ID NO: 7. Second, it appears that the declaration is using KIAA1199 to refer to the protein named with this name in the post-filing date art, see for example GenBank EAW9911.1 whose earliest date of availability was 12/18/06. This molecule is not encoded by the mRNA equivalent of SEQ ID NO: 7, and so the data given in Exhibit 4 of the declaration are not commensurate in scope with the instant claims.

Applicants further argue that they provide additional specific data showing upregulation in the level of expression of KIAA1199 in stool and plasma samples were obtained, relying on the declaration filed 3/26/10 authored by Pedersen. The data in the declaration show that KIAA1199 protein is upregulated in stool samples and serum samples (para 12 an following of declaration). There is not a nexus between this data and the teachings of the specification. In particular, the specification provides only a specific teaching that clones 12-2f and 8-2d (which the specification teach correspond to SEQ ID NO: 7) were detected as upregulated. There is no teaching in the specification that coding portions of the protein referred to as KIAA1199 were detected as upregulated, nor is there any suggestion in the specification that the mRNA equivalent SEQ ID NO: 7 encodes the protein referred to as KIAA1199. Since instant SEQ ID NO: 7 only contains intronic sequence of "the KIAA1199 gene", the mRNA disclosed as

detected in the specification does not encode any portion of this protein. The data given in the declaration regarding the detection of KIAA1199 in blood samples is additional to the specification. Consequently, these data are not sufficient to support the claim portion wherein the sample is stool, blood or serum. The declaration states in paragraph 12 that "increased level of KIAA1199 mRNA transcripts would also have occurred in these stool samples as well." However, it is not known from the experiments which mRNA transcripts would have been detected, as the declaration has previously established that there are multiple mRNA transcripts. The specification only discloses a detection of particular clones which inherently correspond to an intronic portion of the gene, as established in the declaration.

The declaration points to a post-filing date reference, Galamb et al., that reports a microarray analysis of mRNA from colorectal biopsy specimen and peripheral blood of the same patients. First, as noted, the reference was published many years after the filing date of the instant application and cannot be properly used to establish that the claims were enabled at the time of filing. Further, however, the reference highlights that without unpredictable experimentation it is unclear whether a given transcript will have a regulatory pattern that is similar in blood and in the disease tissue. While the reference reports fifty-two genes that were upregulated in both biopsy specimen and peripheral blood of colorectal cancer patients, and three that were similarly downregulated, the reference also reports that in some transcripts the mRNA expression in blood changed in the opposite way compared with their levels in cancer tissue (see page 2841, second column and Table 3). Thus, this exemplifies that it would take significant and unpredictable experimentation to determine if any transcript comprising SEQ ID NO: 7 or expression of any nucleic acid molecule comprising SEQ ID NO: 7 or the complement of SEQ

ID NO: 7 would be differentially expressed in the blood of patients having colorectal adenoma versus healthy controls, such that the a transcript comprising SEQ ID NO: 7 or the complement of SEQ ID NO: 7 could be used in a diagnostic method as claimed.

Applicants point to the declaration at paragraph 13 and Exhibit 4 to support the assertion that one would have expected that gene expression which is altered in colorectal neoplasms would also be detectable in stool and blood samples. The declaration does not provide any direct evidence that detectable levels of an expression product from an mRNA corresponding to SEQ ID NO: 7 is detectable in blood and/or stool. Applicant relies on the assertion that it is well known that all solid tumors are associated with a certain level of apoptosis. The declaration makes a statement regarding "neoplastic colorectal epithelial cells" but adenoma cells are not neoplastic. Further, the instant claims refer to "the onset of colorectal adenoma," and are not directed towards detecting solid tumors, necessarily.

The declaration states in paragraph 14 that it is the author's opinion that once an upregulated expression of a biomarker is established based on tissue biopsy sample, the experimentation involved in confirming that elevated expression can also be detected in stool and blood samples would be routine and not excessive. However, as demonstrated by the Galamb et al. reference, such a showing would remain highly unpredictable. Further, the experimentation involved would be substantial requiring obtaining tissue samples from many patients and controls and conducting experiments whose outcome is uncertain with regard to whether or not the gene would be differentially expressed in blood or stool.

In the final paragraph beginning on page 23, applicant again refers to the data showing elevated levels of expression of KIAA1199 in stool samples. As previously noted, this data is not commensurate in scope with the instant claims.

Applicant states that the figure legend for Figure 1 in Exhibit III of the declaration clearly indicates that the results which are shown are the results of colon tissue specimens from 30 normal, 21 adenoma and 21 cancer patients. This portion of the legend refers to bars (suggesting a bar graph) and Figure 1 in Exhibit 3 of the declaration is a series of scatter plots showing expression of exons of KIAA1199. Neither the level of an mRNA or a protein encoded by said mRNA, wherein said mRNA comprises the mRNA equivalent of SEQ ID NO: 7 appears to be represented in this figure, and so these data are not commensurate in scope with the amended claims.

On page 24 of the remarks, applicant requests that the examiner reconsider her position regarding sample type in light of the actual evidence that these markers are found in the blood, as presented in the declaration. There is no nexus between these data in the declaration and the claims or the teachings in the specification, as previously discussed. Applicant states that the examiner seems to have misunderstood the Declaration, leading to an incorrect conclusion that SEQ ID NO: 7 would not appear in mRNAs. The examiner has made no such mistake, and indicated a claim which utilizes the detection of mRNAs allowable.

The 112 1st paragraph rejection for lack of enablement is maintained.

Claim Rejections - 35 USC § 102

Applicant states that instant SEQ ID NO: 7 was disclosed as SEQ ID NO: 77 in the provisional application. These two sequences are not identical. Instant SEQ ID NO: 7 has 3671 nucleotides while SEQ ID NO: 77 in the provisional application has only 442 nucleotides. Further, identifying SEQ ID NO: 7 in the provisional application is only a starting point for identifying basis for the instantly claimed methods. In particular, the examiner was not able to basis for the currently claimed limitation that an increase in the level of expression of an mRNA that comprises the RNA equivalent of SEQ ID NO: 7 is indicative of the onset of adenoma. The provisional teaches that "differentially regulated" amplicons were marked (p. 69) but never particularly states that SEQ ID NO: 77 or any other sequence had increased expression. Further, it is noted that the Ørntoft et al. reference was applied under 102(a) and 102(b). Even if priority is established for the claimed invention as a whole, the 102(a) rejection would remain. Applicant's arguments regarding priority would not be persuasive if the claims read on the reference. **Nonetheless, the rejections under 102 are withdrawn because of the amendments to the claims.** There is no evidence that the ColoUp1 transcripts identified by Markowitz et al. would measure the level of the RNA equivalent of SEQ ID NO: 7. The mRNA referred to in the prior art as KIAA1199 does not appear to have any identity with instant SEQ ID NO: 7, as previously established on the record. In particular the claims now require that the mRNA detected "comprises the RNA equivalent of SEQ ID NO: 7." Since the amended claims require that the mRNA detected actually comprises the RNA equivalent of SEQ ID NO: 7, the claims do not appear to read on the teachings of Markowitz or Orntoft et al.

Conclusion

The following claim would be allowed if presented in response to this office action:

A method for determining an increased likelihood of the presence of colorectal adenoma in a human, said method comprising

measuring the level of an mRNA which comprises the RNA equivalent of SEQ ID NO: 7 in a gastrointestinal tract sample from said human and

determining an increased likelihood of the presence of colorectal adenoma when the level of said mRNA is increased in said human relative to the normal level of said mRNA in gastrointestinal tract samples from healthy individuals.

7. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C Switzer whose telephone number is (571) 272-0753. The examiner can normally be reached on Monday or Tuesday from 8:30 AM until 5:00 PM, or on Wednesday from 8:00 AM until 1:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached by calling (571) 272-0731.

The fax phone numbers for the organization where this application or proceeding is assigned are (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571)272-0507.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system

provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

/Juliet C. Switzer/
Primary Examiner
Art Unit 1634

November 30, 2010